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LOSS-OF-FUNCTION MUTATION OF THE CARDIAC CAV1.2 CHANNEL IN THE SHORT QT SYNDROME

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Short QT syndrome (SQTS) emerged as a new inherited channelopathy characterized by constantly short QT interval (QTc < 360 ms) associated with atrial fibrillation, syncopal episodes, and/or sudden cardiac death in patients with no underlying structural heart disease. It has been associated with a gain of function in 3 distinct potassium channels (KCNH2, KCNQ1, and KCNJ2) or a loss-of-function of a calcium channel Cav1.2. We identified a 6-year-old male proband who experienced a syncope episode and presented a QTc of 346 ms. In addition, a triangular T wave was observed in V2, V3 leads. His 34-year-old mother was also symptomatic (QTc: 359 ms), with Ventricular fibrillation. The grandmother was asymptomatic (QT: 405 ms). After a screen for ion channel mutations, we found a variant of CACNA1C, gene encoding the α1c of the cardiac L-type calcium channel, leading to c.667G>C transition caused a p.A223P substitution of a mammalian highly conserved residue. This variant was absent in 312 healthy controls.

Cardiac Ca2+ channels are complexes including α1,β, and α2δ subunits allowing the Ca2+ influx (ICaL) essential for excitation-contraction coupling. To evaluate the incidence of this substitution on Cav1.2 function,α1c,β2a, and α2δ1b rat subunits were transfected in HEK-tsA201 cells. The human A223P mutation corresponds to A253P in the rat sequence. Whole-cell patch-clamp experiments were performed to study the mutation effects on ICaL biophysical parameters. A253P Cav1.2 generated a reduced ICaL (-5.48 ± 0.85 Pa/pF, n = 54) in comparison with WT Cav1.2 (-12.24 ± 1.54 Pa/pF, n = 51). The voltage dependence of the Ca2+ current activation did not show any change (V1/2act: −11.54±1.15 mV, n=9, versus −12.94±1.03 mV, n=19; slope: 6.37±0.28 mV versus 6.46±0.27 mV, for mutant and WT channels, respectively). Second, we studied WT and mutant Cav1.2 expression levels. We quantified channels expression by Western blot. The mutated protein was expressed at the same level as WT-Cav1.2. We are currently investigating Cav1.2 addressing to the membrane. In conclusion, we have shown that A253P mutation reduces the ICaL amplitude but the mechanism behind this loss of function remains to be determined.

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SCN5A MUTATIONS AND THE ROLE OF GENETIC BACKGROUND IN THE PATHOPHYSIOLOGY OF BRUGADA SYNDROME

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Background — Brugada syndrome (BrS) is an inherited arrhythmia syndrome with an increased risk of sudden death resulting from polymorphic ventricular tachycardia (VT) and/or ventricular fibrillation (VF) in the absence of gross structural abnormalities. Mutations in SCN5A, encoding the pore-forming subunit α of the cardiac voltage-gated sodium channel, are identified in about 20-30% of probands affected by Brugada syndrome (BrS). SCN5A mutations may also lead to progressive cardiac conduction defects (PCCD). The causality of SCN5A mutations in PCCD was proven by linkage analysis. In contrast, SCN5A mutations in BrS were discovered by a candidate gene approach19 and linkage data are still lacking.

The aim of this study was to investigate the association of SCN5A mutations and BrS in a group of large genotyped families.

Methods and Results — Families were included if at least 4 family members were carriers of the SCN5A mutation identified in the proband.

Thirteen large families composed by 115 mutation-carriers were studied. The signature type I ECG was present in 54 mutation-carriers (BrS-ECG+) (47%). In 5 families, we found 7 individuals affected by BrS, but with a negative genotype (mutation-negative BrS-ECG+). Among these 7 mutation-negative BrS+ individuals, 3, belonging to 3 different families, had a spontaneous type I ECG, while 4 had a type I ECG after administration of Na+ channel blockers. EPS was performed in 5 BrS-ECG non-mutation patients. Ventricular tachyarrhythmias were inducible in 3. An ICD was implanted in these 3 patients. Mutation carriers (n=115) had, on average, longer PR and QRS intervals than non-carriers (n=148) demonstrating that these mutations exerted functional effects.

Conclusions — Our results suggest that SCN5A mutations might not be sufficient to cause BrS and that genetic background may play a powerful role in the pathophysiology of BrS. However, this study confirms the role of SCN5A mutations in PCCD.

These findings add further complexity to concepts regarding the causes of BrS, and are consistent with the emerging notion that the pathophysiology of BrS includes various elements beyond mutant sodium channels.

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IMPLICATION DES CANAUX KATP DANS LE SYNDROME DE REPOLARISATION PRÉCOCE

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